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PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 21 August 2001 (21.08.01)	
International application No. PCT/IT00/00424	**Applicant's or agent's file reference** 00 OT 22E
International filing date (day/month/year) 20 October 2000 (20.10.00)	**Priority date** (day/month/year) 21 October 1999 (21.10.99)
Applicant SENECI, Alessandro et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

16 May 2001 (16.05.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Zakaria EL KHODARY

Telephone No.: (41-22) 338.83.38

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

RECORD COPY

For receiving Office use only

PCT/IT 00 / 00424
International Application No.

20 OCT 2000 20 1000
International Filing Date

MINISTERO INDUSTRIA, COMMERCIO e ARTIGIANATO
Direzione Generale per lo sviluppo produttivo e la competitività
- Ufficio italiano brevetti e marchi -
DIV. VII - BREVETTO EUROPEO - PCT
Via Molise, 19 - 00187 ROMA
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 00 OT 22 E

Box No. I TITLE OF INVENTION

Gastroresistant tablets for alimentary, dietetic and therapeutic use

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

TRUFFINI & REGGE' FARMACEUTICI SRL
Via Oslavia 18
20134 MILANO - Italy

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: IT

State *(that is, country)* of residence: IT

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SENECI Alessandro
Via F.lli Cervi - Res. del Parco
20090 Segrate (MI2) - Italy

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: IT

State *(that is, country)* of residence: IT

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PISTOLESI ROBERTO
DRAGOTTI & ASSOCIATI SRL
Galleria San Babila 4/C
20122 MILANO - Italy

Telephone No.
02 799340

Facsimile No.
02 784427

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

CONFIRMATION COPY

PCT/IT00/00424

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ALBERICO Pia
Via Martino Anzi, 15
22100 - Como - Italy

This person is:
- [ ] applicant only
- [x] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: IT

State *(that is, country)* of residence: IT

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [x] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
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Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

- [ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* . . . . . .

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

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☒ **AL** Albania . . . . . .
☒ **AM** Armenia . . . . . .
☒ **AT** Austria . . . . . .
☒ **AU** Australia . . . . . .
☒ **AZ** Azerbaijan
☒ **BA** Bosnia and Herzegovina . . . . . .
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☒ **CR** Costa Rica . . . . . .
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☒ **DE** Germany . . . . . .
☒ **DK** Denmark . . . . . .
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☒ **EE** Estonia . . . . . .
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☒ **UA** Ukraine . . . . . .
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☒ **US** United States of America . . . . . .
☒ **UZ** Uzbekistan . . . . . .
☒ **VN** Viet Nam . . . . . .
☒ **YU** Yugoslavia . . . . . .
☒ **ZA** South Africa . . . . . .
☒ **ZW** Zimbabwe . . . . . .

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ DZ Algeria . . . . . ☒ MZ Mozambique . . . . . .
☒ BZ Belize . . . . . .

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

*1. If, in any of the Boxes, **the space is insufficient** to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

*(i) **if more than two persons are involved as applicants and/or inventors** and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*

*(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "**the States indicated in the Supplemental Box**" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

*(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, **the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America**: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

*(iv) if, in addition to the agent(s) indicated in Box No. IV, there are **further agents**: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

*(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "**patent of addition**," or "**certificate of addition**," or if, in Box No. V, the name of the United States of America is accompanied by an indication "**continuation**" or "**continuation-in-part**": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*

*(vi) if, in Box No. VI, there are **more than three earlier applications whose priority is claimed**: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;*

*(vii) if, in Box No. VI, **the earlier application is an ARIPO application**: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed.*

*2. If, with regard to the **precautionary designation statement** contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

*3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning **non-prejudicial disclosures or exceptions to lack of novelty**: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.*

Continuation of Box No. IV:

DRAGOTTI GIANFRANCO MICHELOTTI GIULIANO FERRONI FILIPPO	all of	DRAGOTTI & ASSOCIATI SRL Galleria San Babila 4/C 20122 MILANO - Italy
AGOSTINI AGOSTINO	of	DRAGOTTI & ASSOCIATI SRL Via Paris Bordone 9 31100 TREVISO - Italy

PCT/IT00/00424

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 21/10/1999	MI99A002206	IT		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): _____

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* :

ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 5
description (excluding sequence listing part)	: 12
claims	: 3
abstract	: 1
drawings	:
sequence listing part of description	:
Total number of sheets	: 21

This international application is **accompanied by** the item(s) marked below:

1. ☐ fee calculation sheet
2. ☒ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☒ translation of international application into (language): ENGLISH
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

4 RO

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: Italian

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Milan, 20 October 2000

Roberto Pistolesi

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1. Date of actual receipt of the purported international application: 20 OCT 2000 20 10 00
2. Drawings: ☐ received: ☒ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

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Date of receipt of the record copy by the International Bureau: 28 NOVEMBER 2000 28 NOV 2000

Compresse gastroresistenti ad uso alimentare, dietetico o terapeutico

II presente trovato si riferisce a delle formulazioni gastroresistenti, preferibilmente compresse, ad uso alimentare o dietetico ottenute con grasso miscelato alla massa per consentire una cessione prolungata nell'organismo dei principi attivi in esse contenuti.

La preparazione delle formulazioni gastroresistenti viene abitualmente eseguita per consentire al principio attivo di essere rilasciato ed assorbito secondo modalità più o meno ritardate a livello intestinale; alternativamente, il principio attivo potrà essere rilasciato ed assorbito solo parzialmente a livello gastrico, consentendo il rilascio e l'assorbimento di una seconda frazione del principio attivo a livello intestinale.

La tecnica nota per la preparazione di formulazioni a rilascio ritardato gastroresistenti è la seguente:

A) Formulazioni gastro-resistenti: si tratta di compresse rivestite con vernici gastroresistenti come, ad esempio, etil cellulosa, acetoftalato di cellulosa, poliacrilati, gomma lacca, cheratina; le compresse verniciate vengono poi confettate con zucchero.

B) Formulazioni a strati: si preparano come i confetti gastro-resistenti, per quello che concerne la verniciatura delle compresse; sul nucleo verniciato viene fatta aderire a lamina una polvere aspersola come l'amido o il talco, in cui si disperde un principio attivo usando come collante un prodotto idrosolubile come, ad esempio, gomma arabica, agar-agar ecc., in modo tale

che nello stomaco si sciolga lo strato più esterno e non la compressa interna.

C) Capsule con cronoidi; si tratta di anime zuccherine su cui viene disperso il principio attivo e poi una vernice protettiva come al punto A);

D) Compresse in cui vengono dispersi cronoidi in modo che una parte del principio attivo sia nei cronoidi gastroresistenti e parte nella compressa idrodispersibile;

E) Compresse a più strati, in cui uno o più strati contengono polveri ritardanti lo scioglimento, quali gomme lacche derivate dalla cellulosa in modo che gli lo strati abbiano una diversa solubilità.

Si tratta in generale di formulazioni che basano il proprio effetto ritardante sull'impiego di eccipienti e/o coadiuvanti estranei all'organismo dei mammiferi, in particolare dell'uomo, con i quali si cerca di massimizzare l'assorbimento del principio attivo senza tenere conto dei normali processi fisiologici digestivi.

L'impiego di simili sostanze è tuttavia normalmente poco desiderabile, in particolare nel caso di formulazioni dietetiche e/o nel caso di integratori alimentari, dove si cerca invece di ottenere un assorbimento del principio attivo secondo un profilo cinetico che si avvicini il più possibile ai normali processi digestivi dell'uomo.

Il ricorso a profili di assorbimento "naturali" è comunque desiderabile anche nel caso di formulazioni terapeutiche, ad esempio in tutte quelle categorie di malati che potrebbero ricevere un danno dalla somministrazione di eccipienti e/o coadiuvanti non "fisiologici"; basti

ad esempio pensare alle donne in stato interessante, ai bambini molto piccoli, ai soggetti allergici, ecc..

E' stata ora trovata, e costituisce l'oggetto della presente invenzione, una nuova formulazione a rilascio ritardato che consente l'assorbimento dei principi attivi sfruttando l'attività digestiva fisiologica, ovvero mimando quanto avviene con i cibi usualmente ingeriti.

La presente invenzione ha infatti per oggetto una formulazionein forma di compressa per uso orale contenente almeno un principio attivo ad azione farmaceutica, dietetica o alimentare in combinazione con almeno un grasso e/o un fosfolipide, quale veicolante, in quantità compresa tra il 5 ed il 30% rispetto al peso della formulazione stessa; preferibilmente, tali grassi e/o fosfolipidi sono presenti in quantità compresa tra il 20 e il 30% rispetto al peso della formulazione.

Gli acidi grassi contenuti nei grassi e nei fosfolipidi utilizzabili per gli scopi della presente sono normalmente selezionati tra quelli contenenti acidi grassi idrogenati e non idrogenati, sia di origine sintetica che naturale, aventi catena compresa tra 3 e 20 atomi di carbonio, preferibilmente tra 14 e 18 atomi di carbonio, e loro miscele.

Una lista non limitativa di tali acidi comprende ad esempio l'acido palmitico, l'acido stearico, l'acido miristico, l'acido laurico, l'acido caprilico e l'acido caprico ecc..

Da un punto di vista pratico, i grassi possono essere normalmente selezionati tra burro di cacao, olio di palma idrogenato, grassi vegetali

idrogenati come il burro di arachide, grassi animali come strutto, burro, lardo da soli o in miscela tra di loro.

I fosfolipidi sono invece preferibilmente utilizzati come lecitine e, in particolare, come lecitina di soia. Eventualmente, i suddetti grassi e fosfolipidi possono essere usati in combinazione con i sali di metalli alcalini e/o alcalino terrosi di acidi grassi aventi catena compresa tra 3 e 20 atomi di carbonio, preferibilmente tra 14 e 18 atomi di carbonio, o loro miscele; i sali preferiti sono quelli di sodio, potassio e calcio.

Come abbiamo precedentemente accennato, i principi attivi utilizzabili per gli scopi della presente invenzione possono avere sia azione terapeutica che dietetica o alimentare. I principi attivi ad azione terapeutica possono essere scelti tra i farmaci anti-infiammatori non steroidei (NSAID) e steroidei, tranquillanti, sonniferi, farmaci anti-ipertensivi, anti-istaminici ed anti-asmatici; i farmaci anti-infiammatori non steroidei sono a loro volta selezionabili tra ibuprofene, naproxene, ketoprofene, indometacina, acido acetilsalicilico, acido mefenamico, acido flufenamico, ecc.; i principi attivi ad azione dietetica o alimentare possono essere scelti nel gruppo costituito da fermenti lattici, lievito di birra sia tal quale che con cellule vitali, vitamine, minerali, amminoacidi, estratti vegetali e loro derivati.

Nella formulazione secondo la presente invenzione, il principio o i principi attivi, che possono essere utilizzati sia come tali che sotto forma di esteri o di sali fisiologicamente accettabili, possono essere miscelati direttamente con detto almeno un grasso e/o fosfolipide,

senza l'aggiunta di eventuali eccipienti e/o coadiuvanti; in questo caso, il principio o i principi attivi costituiscono il 70-95% in peso della formulazione, preferibilmente il 75-90%.

Alternativamente, i suddetti principi attivi possono essere impiegati in combinazione con i normali eccipienti e/o coadiuvanti noti nell'arte; in questo caso, essi sono normalmente presenti in quantità compresa tra l'1 ed il 50%, preferibilmente tra il 10 ed il 40%, rispetto al peso complessivo della formulazione.

Gli eccipienti utilizzati per la compressa della presente invenzione possono essere scelti nel gruppo costituito da amidi, maltodestrine, cellulose microcristalline, cellulose modificate talco, calcio carbonato, proteine del latte, stearati di calcio, magnesio, sodio, proteine di soia o adatte polveri inerti, PVP, silice precipitata e sono presenti in una quantità del 10-30% in peso, preferibilmente del 20-30%, rispetto al peso complessivo della formulazione.

Per valutare l'attività di rilascio nel tempo di un principio attivo contenuto in una formulazione secondo la presente invenzione (la cui composizione quali-quantitativa è riportata nell'esempio 1), si è eseguito il test di dissoluzione riportato nella Farmacopea Ufficiale Italiana, il cui risultato è riferito nella seguente Tabella.

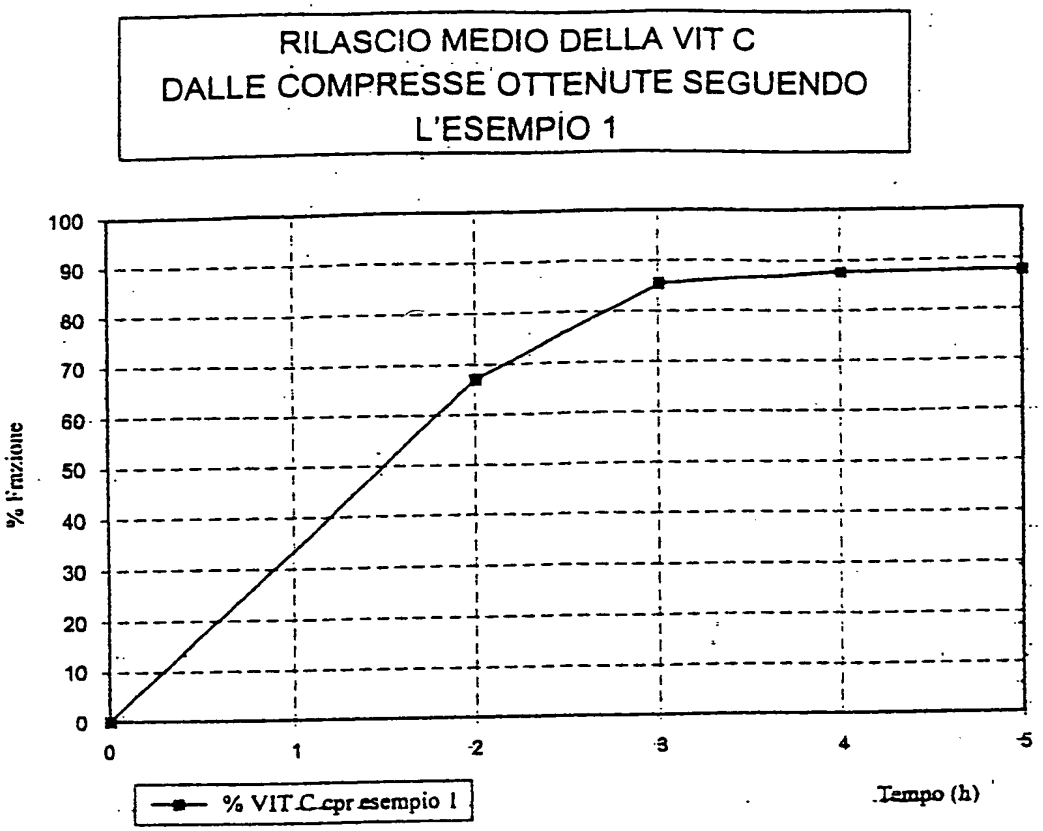

TABELLA I

Da questo test di dissoluzione si può constatare il lento rilascio nel tempo di un principio attivo nelle condizioni fisiologiche che simulamo i processi digestivi che normalmente avvengono nello stomaco.

La presente invenzione è particolarmente adatta alla realizzazione di compresse gastroresistenti a certificazione BIO, purché si usino dei grassi derivanti da coltivazioni e allevamenti biologici secondo le vigenti normative.

Un ulteriore oggetto della presente invenzione è inoltre costituito dal procedimento per la preparazione delle formulazioni secondo la presente invenzione.

Detto procedimento è costituito dalla premiscelazione di un principio attivo come precedentemente definito, in una quantità del 1-50% in peso rispetto al peso complessivo della formulazione, con gli eccipienti come precedentemente definiti, a loro volta presenti in una quantità del 10-30% rispetto al peso complessivo della formulazione. La miscela cosi ricavata per semplice miscelazione a temperatura ambiente o per granulazione a secco o a umido secondo la tecnica nota, è impastata con un adatto impastatore, generalmente a zeta o a braccia tuffanti, con almeno un grasso e/o un fosfolipide allo stato fuso in quantità compresa tra il 5 ed il 30% rispetto al peso della formulazione stessa.

L'impasto così ottenuto viene raffreddato a 5-20° C, preferibilmente a 10° C-12° C, e viene quindi granulato ad esempio mediante granulatore oscillante di tipo Manesty, munito di lamiera inox forata con fori di diametro tra 1-4 mm, preferibilmente 1-2 mm.

Il granulato così ottenuto viene compresso con comprimitrice rotativa munita di adatti punzoni. Si possono in questo modo ottenere delle compresse di peso opportuno.

Nel caso di compresse non contenenti eccipienti e/o coadiuvanti aggiuntivi, il principio attivo viene miscelato direttamente con il grasso e/o fosfolipide allo stato fuso; la miscela viene poi lavorata come sopra descritto.

In particolare la presente invenzione è molto adatta alla preparazione di compresse a strati ottenute con una comprimitrice adatta quale per esempio una Manesty BB3B.

Il procedimento consiste nel comprimere uno strato ottenuto secondo la tecnica nota usando uno o più principi attivi miscelati con noti eccipienti idrosolubili o idrodispersibili, e uno strato ottenuto secondo la presente invenzione. Eventualmente si possono utilizzare anche più di due strati con diverso grado di solubilità.

I seguenti esempi vengono riportati per meglio descrivere la presente invenzione senza tuttavia limitarne la portata

Esempio 1

Si preparano 1000 compresse formate da uno strato a rapida dissoluzione (Strato A) ottenuto impastando in impastatrice a zeta con Kllucel/Acqua 10% i seguenti componenti:

prolina (100 gr),

lisina (100 gr),

cistina (100 gr),

CMC sodica (20 gr)

L'impasto così ottenuto si essicca per 12 ore a 40°C in essiccatore ad armadio, quindi si granula con granulatore Manesty munito di lamiera inox forata con un diametro di 2 mm per una resa di 321,8 g.

Il granulato così ottenuto è miscelato in un miscelatore a coclea rotante (SAGA) con :

lacca rossa red n° 40 all lake (0,25 g),

vitamina A 5000000 UI/g (800 mcg/cpr +30%) (2,31 g),

vitamina E 50%SD (16 mg/cpr +20%) (12,8 g),

vitamina C granulare (49,5 g),

magnesio stearato (5 g),

rame gluconato 14% (1,2 mg/cpr + 5%) (6 g),

zinco gluconato 13,4% (10 mg/cpr + 5%) (52,2 g)

lievito al selenio 2000 mcg/g (0,055 mcg/cpr + 5%) (19 g)

glutatione su lievito (25 mg/cpr + 20%) (15 g),

PVP a rapida disgregazione (20 g),

amido di patata (10 g),

gel di silice (3 g),

maltodestrina (5 g),

cellulosa microcristallina (2 g),

acqua (0,5 g),

per una resa totale di 524,36 g.

Si prepara una seconda miscela che andrà a costituire lo strato a lenta dissoluzione (STRATO B) così ottenuto:

mirtillo liofilizzato (15 g),

cellulosa microcristallina (50 g),

Titanio biossido (10 g),

Acidi nucleici (50 g),

Estratto di mirtillo 25% (50 g),

Rame gluconato (1,5 g),

Zinco gluconato (12,3 g),

Rame gluconato (1,5 g),

Zinco gluconato (13,8 g),

Lievito al selenio (9,5 g),

Glutatione su lievito (15 g),

Vitamina A 500000 UI/g (4,63 g),

Vitamina E 50% SD (25,6 g),

Vitamina C EC 97% (99 g),

Tutti questi componenti vengono miscelati e impastati in impastatrice a zeta con l'olio di palma idrogenato fuso (50 gr).

L'impasto ottenuto si raffredda a 12°C e si granula con granulatore oscillante munito di lamiera inox forata con diametro di 2 mm per una resa totale di 408 g.

Le due miscele così ricavate possono essere compresse con punzone ovale mediante una comprimitrice a due strati (MANESTY BB3B) facendo compresse ovali del peso di 0,932 g in cui il primo strato di 0,524 g è a rapida dissoluzione ed il secondo di 0,408 g è gastroresistente e a lenta dissoluzione.

Esempio 2

Si opera come nell'esempio 1 ma utilizzando i seguenti componenti:

Strato A (A RAPIDA DISSOLUZIONE)

Acido folico 98% (0,3 mg/cpr + 20%) (0,12 g)

Vitamina B6 33,1/3 (1,5 mg + 20%) (1,8 g)

Betacarotene 20% (4mg/cpr + 10%) (7,4 g)

Vitamina E 50% SD (116 mg/cpr) (12,8 g)

Vitamina C EC 97 (120 mg/cpr +20%) (49,5 g)

Rame gluconato Cu 14% (1,2 mg/cpr) (6 g)

Zinco gluconato Zn 13,4% (10 mg/cpr) (52,3 g)

Lievito al selenio 2000 mcg/g (55 mcg/cpr) (19,3 g)

Lattosio CD (150 g)

Cellulosa microcristallina (30 g)

Acqua (4 g)

Amido di patate (30 g)

PVP a rapida disgregazione (Kollidon CL) (10 g)

Gel di silice (10 g)

Maltodestrina (8g)

per un totale di 391,22 g:

Strato B (A LENTA DISSOLUZIONE)

Solfomucopolisaccaridi (25 g)

Ginko biloba (30 g)

Rame gluconato Cu 14% (3 g)

Zinco gluconato Zn 13,4% (26,2 g)

Lievito al selenio 2000 mcg/g (9,7 g)

Cellulosa microcristallina (50 g)

Ferro ossido rosso (5 g)

Acido folico (0,24 g)

Vitamina B6 33,1/3% (3,6 g)

Vitamina E 50% (25,6 g)

Vitamina C EC 97% (99 g)

Betacarotene 20% (14,8 g)

Olio di palma idrogenato fuso (72 g)

Gel di silice (0,5%),

per un totale di 0,358 g.

Si fanno compresse a due strati da 0,749 g di cui il primo strato, a rapida dissoluzione, di 0,391 g ed il secondo, a lenta dissoluzione, di 0,358 g.

Le compresse possono essere poi verniciate con una soluzione di Klucel/Acqua 10 %.

Esempio 3

Si procede come per l'esempio 1 ma utilizzando i seguenti componenti:

Strato A (A RAPIDA DISSOLUZIONE)

Acido acetilsalicilico	0.3 g
Olio di palma idrogenato	0.1 g
Lattosio	0.2 g

Strato B (A LENTA DISSOLUZIONE)

Acido acetilsalicilico	0.2 g
Lattosio	0.1 g
Magnesio stearato	0.01 g
amido di mais preessiccato	0.1 g

RIVENDICAZIONI

1. Una formulazione per uso orale in forma di compressa contenente almeno un principio attivo ad azione farmaceutica, dietetica o alimentare caratterizzata dal contenere, quale veicolante, almeno un grasso e/o un fosfolipide in quantità compresa tra il 5 ed il 30%, preferibilmente tra il 10 e il 20%, rispetto al peso della formulazione stessa.

2. Una formulazione secondo la rivendicazione 1 caratterizzata dal fatto che detto almeno un grasso e/o un fosfolipide contiene acidi grassi idrogenati e non idrogenati, sia di origine sintetica che naturale, aventi catena compresa tra 3 e 20 atomi di carbonio, preferibilmente tra 14 e 18 atomi di carbonio, o loro miscele.

3. Una formulazione secondo la rivendicazione 1 caratterizzata dal fatto che detto almeno un grasso e/o un fosfolipide è selezionato tra burro di cacao, olio di palma idrogenato, grassi vegetali idrogenati come il burro di arachide, grassi animali come strutto, burro, lardo, e che detti fosfolipidi sono selezionati tra le lecitine, preferibilmente di soia.

4. Una formulazione secondo la rivendicazione 1 caratterizzata dal fatto che detto almeno un grasso e/o un fosfolipide è impiegato in combinazione con i sali di metalli alcalini e/o alcalino terrosi di acidi grassi aventi catena compresa tra 3 e 20 atomi di carbonio, preferibilmente tra 14 e 18 atomi di carbonio, o loro miscele.

5. Una formulazione secondo la rivendicazione 1 caratterizzata dal fatto che detto almeno un principio attivo è presente in quantità del 70-95%, preferibilmente del 75-90%, rispetto al peso della formulazione, e che detto

almeno un principio attivo e detto almeno un grasso e/o fosfolipide costituiscono il 100% in peso della formulazione.

6. Una formulazione secondo la rivendicazione 1 caratterizzata dal fatto che detto almeno un principio attivo ad azione terapeutica è scelto tra i farmaci anti-infiammatori non steroidei e steroidei, tranquillanti, sonniferi, farmaci anti-ipertensivi, anti-istaminicied anti-asmatici e che detto almeno un principio attivo ad azione dietetica o alimentare è scelto nel gruppo costituito da fermenti lattici, lievito di birra sia tal quale che con cellule vitali, vitamine, minerali, amminoacidi, estratti vegetali e loro derivati.

7. Una formulazione secondo la rivendicazione 1 contenente: (a) dall' 1 al 50% in peso, preferibilmente dal 30 al 50%, di detto almeno un principio attivo ad azione farmaceutica, dietetica o alimentare; (b) dal 5 al 30% in peso, preferibilmente dal 20 al 30%, di detto almeno un grasso e/o fosfolipide; (c) dal 10 al 30% in peso, preferibilmente dal 20 al 30%, di eccipienti e/o coadiuvanti; dove la somma dei componenti (a), (b) e (c) costituisce il 100% in peso della formulazione.

8. Una formulazione secondo la rivendicazione 7 caratterizzata dal fatto che detti eccipienti sono selezionati tra amidi, maltodestrine, cellulose microcristalline, cellulose modificate talco, calcio carbonato, proteine del latte, stearati di calcio, magnesio, sodio, proteine di soia o adatte polveri inerti, PVP, silice precipitata.

9. Un procedimento per la preparazione di una formulazione secondo la rivendicazione 5 in cui:

a) detto almeno un principio attivo è mescolato con detto almeno un grasso e/o un fosfolipide allo stato fuso nei rapporti ponderali sopra definiti;

b) l'impasto così ottenuto viene raffreddato a 5-20° C, preferibilmente a 10°C-12°C, e viene quindi granulato mediante granulatore con fori di diametro compreso tra 1 e 4 mm, preferibilmente tra 1 e 2 mm;

c) il granulato così ottenuto viene quindi compresso.

10. Un procedimento per la preparazione di una formulazione secondo la rivendicazione 7 in cui:

d) detto almeno un principio attivo è premiscelato a temperatura ambiente con detti eccipienti e/o coadiuvanti nei rapporti ponderali sopra definiti;

e) la miscela cosi ricavata è mescolata con detto almeno un grasso e/o un fosfolipide allo stato fuso nei rapporti ponderali sopra definiti;

f) l'impasto così ottenuto viene raffreddato a 5-20° C, preferibilmente a 10°C-12°C, e viene quindi granulato mediante granulatore con fori di diametro compreso tra 1 e 4 mm, preferibilmente tra 1 e 2 mm;

g) il granulato così ottenuto viene quindi compresso.

Riassunto

Viene descritta una nuova formulazione per uso orale contenente almeno un principio attivo ad azione farmaceutica, dietetica o alimentare in combinazione con almeno un grasso e/o un fosfolipide in quantità compresa tra il 5 ed il 30% rispetto al peso della formulazione stessa; tale formulazione consente il lento rilascio nel tempo del principio attivo nelle condizioni fisiologiche che simulamo i processi digestivi che normalmente avvengono nello stomaco.

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/IT 00/00424

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 305 604 A (QUEST VITAMINS) 16 April 1997 (1997-04-16) claims ---	1,3-8
X	US 4 374 082 A (R.HOCHSCHILD) 15 February 1983 (1983-02-15) claims examples column 2, line 62 - line 65 column 3, line 34 - line 45 column 4, line 3 - line 29 ---	1,3,5-7
X	DE 39 14 622 A (E.FIEGERT-SEIBT) 8 November 1990 (1990-11-08) claims examples column 1, line 40 - line 46 column 2, line 55 - line 62 --- -/--	1,3,6,9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 May 2001	18/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In. .ational Application No
PCT/IT 00/00424

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 35656 A (R.P.SCHERER) 20 August 1998 (1998-08-20) claims examples ---	1-10
A	WO 95 05808 A (ABBOTT) 2 March 1995 (1995-03-02) claims -----	1-10

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IT 00/00424

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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Gastroresistant tablets for alimentary, dietetic and therapeutic use

The present invention relates to gastro-resistant formulations, preferably tablets, for alimentary or dietary use, which are obtained by mixing the composition with fat in order to achieve a prolonged release of the active principles contained therein to the organism.

The preparation of the gastro-resistant formulations is usually carried out so as to allow the active principle to be released and absorbed in a more or less retarded manner at the intestine level; alternatively, the active principle may be released and absorbed only in part at the stomach level, thus allowing a second fraction of the active principle to be released and absorbed at the intestine level.

The known technique for preparing gastro-resistant formulations with retarded release is as follows:

A) Gastro-resistant formulations: these are tablets lined with gastro-resistant films, such as, for example, ethylcellulose, cellulose acetophthalate, polyacrylates, gum lac, keratine; the lined tablets are then coated with sugar.

B) Layered formulations: they are prepared in the same manner as the gastro-resistant sugar-coated pills, with regard to coating of the tablets; a sprinkling powder such as starch or talcum, in which an active principle is dispersed using a water-soluble product such as gum arabic, agar-agar etc. as the adhesive, is attached layerwise to the coated core, in such a manner that the outermost layer and not the inner tablet is dissolved in the stomach.

C) Capsules containing retarding agents; they are sugar cores in which the active principle is dispersed, followed by application of a protective coating as in para. A);

D) Tablets in which retarding agents are dispersed in such a way that part of the active principle is present in the gastro-resistant retarding agents and part is present in the water-dispersible tablet;

E) Multi-layered tablets in which one or more layers contain dissolution-retarding powders, such as cellulose-derived gum lacs so that the layers have different solubilities.

In general, they are formulations whose retarding effect is based on the use of excipients and/or adjuvants foreign to the mammalian organism, in particular of humans, which formulations are intended to maximize the absorption of the active

principle without taking into consideration the normal physiological digestive processes.

However, the use of such substances is usually not very desirable, in particular in the case of dietary formulations and/or in the case of food additives which are intended to achieve instead an absorption of the active principle according to a kinetic profile which is as close as possible to the normal human digestive processes.

The recourse to "natural" absorption profiles is anyway desirable, even in the case of therapeutic formulations, for example in all those classes of patients who would be harmed by administering them non-"physiological" excipients and/or adjuvants; obvious examples are pregnant women, very young children, allergic subjects, etc.

Now, according to the subject-matter of the present invention, a novel fomulation with retarded release has been found, said formulation allowing the active principles to be absorbed utilizing the physiological digestive activity, i.e. imitating what happens with food ingested in the usual manner.

The present invention relates to a formulation in tablet form for oral use, containing at least one active principle with a pharmaceutical, dietary or alimentary action in combination with at least one fat and/or phospholipid, as the vehicle, in an amount of between 5 und 30%, relative to the weight of the formulation; preferably, such fats and/or phospholipids are present in an amount of between 20 and 30%, relative to the weight of the formulation.

The fatty acids contained in the fats and phospholipids which can be used for the purposes of the present invention are normally selected from those containing hydrogenated and non-hydrogenated fatty acids, either of synthetic or natural origin, having a chain comprising between 3 and 20 carbon atoms, preferably between 14 and 18 carbon atoms, and mixtures thereof.

A non-limiting list of such acids comprises, for example, palmitic acid, stearic acid, myristic acid, lauric acid, caprylic acid, capric acid, etc.

From a practical point of view, the fats can normally be selected from among cocoa butter, hydrogenated palm oil, hydrogenated vegetable fats such as peanut butter, animal fats such as lard, butter, bacon fat separately or in a mixture thereof.

The phospholipids are instead preferably used as lecithins and, in particular, as soya lecithin. If desired, the abovementioned fats and phospholipids may also be

used in combination with alkali metal salts and/or alkaline earth metal salts of fatty acids having a chain comprising between 3 and 20 carbon atoms, preferably between 14 and 18 carbon atoms, or mixtures thereof, the preferred salts being those of sodium, potassium and calcium.

As indicated above, the active principles which can be used for the purposes of the present invention may have both a therapeutic and a dietary or alimentary action. The active principles with a therapeutic action may be selected from among non-steroid anti-inflammatory drugs (NSAID) and steroid anti-inflammatory drugs, tranquilizers, sleeping pills, anti-hypertensive, anti-histaminic and anti-asthmatic drugs; non-steroid anti-inflammatory drugs in turn may be selected from among ibuprofen, naproxen, ketoprofen, indomethacin, acetylsalicylic acid, mefenamic acid, flufenamic acid, etc.; the active principles with a dietary action may be selected from the group consisting of lactic acid microorganisms, beer yeasts, either as such or containing living cells, vitamins, minerals, amino acids, vegetable extracts, and derivatives thereof.

In the formulation according to the present invention, the active principle or principles, which may be used as such or in the form of esters or physiologically acceptable salts, can be mixed directly with said at least one fat and/or phospholipid without the addition of any excipients and/or adjuvants; in this case, the active principle or principles make up 70-95% by weight, preferably 75-90% by weight, of the formulation.

Alternatively, the abovementioned active principles may be used in combination with customary excipients and/or adjuvants known in the art; in this case, they are normally present in amounts of between 1 and 50%, preferably between 10 and 40%, relative to the total weight of the formulation.

The excipients used for the tablet accordintg to the present invention may be selected from the group consisting of starches, maltodextrin, microcrystalline cellulose, talcum-modified cellulose, calcium carbonate, milk proteins, calcium stearate, magnesium stearate, sodium stearate, soya proteins or suitable inert powders, PVP, precipitated silica and are present in an amount of 10-30% by weight, preferably 20-30% by weight, relative to the total weight of the formulation.

In order to determine the release activity, over time, of an active principle contained in a formulation according to the present invention (the qualitative and quantitative composition of which is given in Example 1), the dissolution test described in Farmacopea Ufficiale Italiana (Official Italian Pharmacopeia) was carried out. The results of said test are shown in the table below.

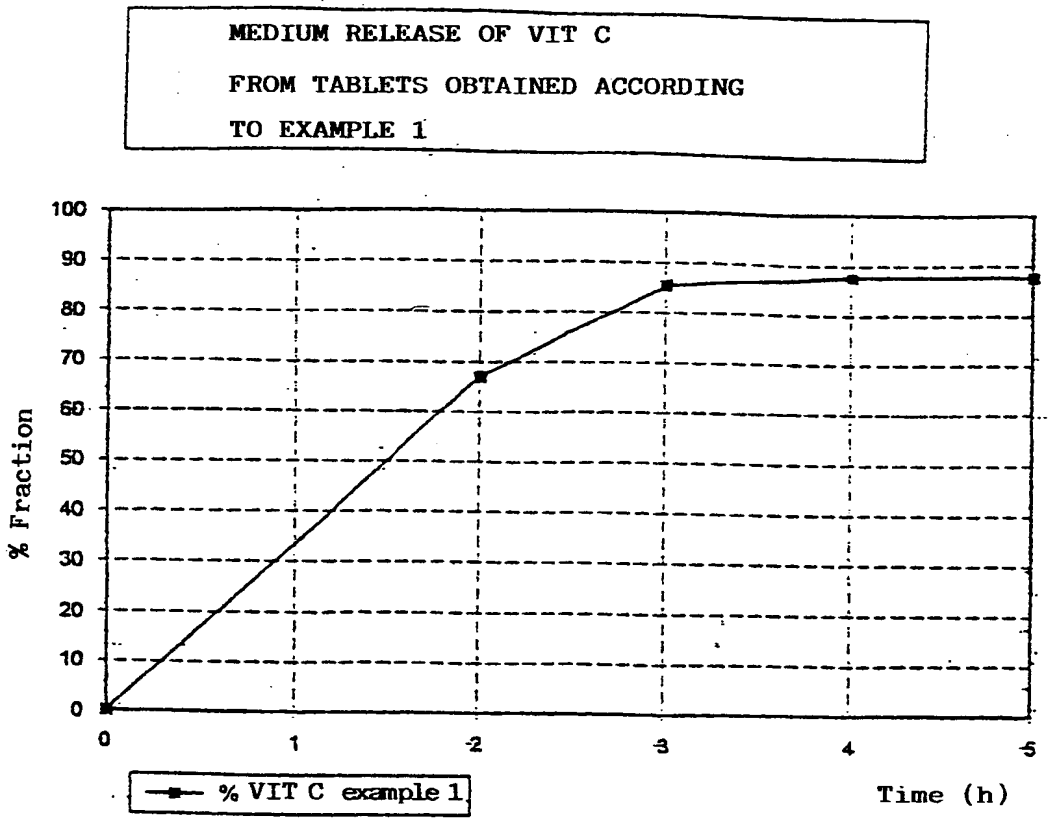

TABLE I

This dissolution test demonstrates the slow release, over time, of an active principle under physiological conditions which simulate the digestive processes which normally take place in the stomach.

The present invention is particularly suitable for the production of BIO-certified gastro-resistant tablets, provided that fats derived from biological cultivations and farms in accordance with current regulations are used.

The present invention furthermore relates to the process for the preparation of the formulations according to the present invention.

Said process comprises premixing an active principle as defined above in an amount of 1-50% by weight, relative to the total weight of the formulation, with the excipients as defined above, which in turn are present in an amount of 10-30%, relative to the total weight of the formulation. The mixture thus obtained by simple mixing at ambient temperature or by dry or wet granulation in accordance with the known technique is kneaded in a suitable kneader, usually a Z-type kneader or plunging-arm kneader, together with at least one fat and/or phospholipid in the melted state in an amount of between 5 and 30%, relative to the weight of the formulation.

The blend thus obtained is cooled to 5-20° C, preferably to 10°C-12° C, and then granulated, for example using an oscillating granulator of the Manesty type equipped with a perforated stainless steel plate having holes with a diameter of 1-4 mm, preferably 1-2 mm.

The granules thus obtained are compressed with a rotary tablet-compressing machine equipped with suitable punches. It is thus possible to obtain tablets of suitable weight.

In the case of tablets not containing added excipients and/or adjuvants, the active principle is mixed directly with the fat and/or phospholipid in the melted state; the mixture is then processed as described above.

In particular, the present invention is highly suitable for the preparation of layered tablets obtained with a suitable tablet-compressing machine such as, for example, a Manesty BB3B.

The process consists in compressing a layer obtained according to the prior art using one or more active principles mixed with known water-soluble or water-dispersible excipients and one layer obtained according to the present invention. If

desired, it is also possible to use more than two layers with different degrees of solubility.

The examples which follow are given in order to describe better the present invention without, however, limiting its scope.

Example 1

1000 tablets are prepared, being formed by a fast-dissolving layer (Layer A) obtained by kneading, in a Z-type kneader, the following components together with 10% strength Klucel/water:

proline (100 g),

lysine (100 g),

cystine (100 g),

sodium carboxymethylcellulose (20 g)

The blend thus obtained is dried for 12 hours at 40°C in a drying cabinet, the resulting mixture is granulated in a Manesty granulator equipped with a perforated stainless steel plate having holes with a 2-mm diameter, giving a yield of 321.8 g.

The granules thus obtained are mixed in a rotating-screw mixer (SAGA) with :

red lake N° 40 all lake (0.25 g),

vitamin A 5,000,000 IU/g (800 μg/cpr +30%) (2.31 g),

vitamin E 50% SD (16 mg/cpr +20%) (12.8 g),

vitamin C granules (49.5 g),

magnesium stearate (5 g),

copper gluconate Cu 14% (1.2 mg/cpr + 5%) (6 g),

zinc gluconate Zn 13.4% (10 mg/cpr + 5%) (52.2 g)

selenium-containing yeast 2,000 μg/g (0.055 μg/cpr + 5%) (19 g)

glutathione on yeast (25 mg/cpr + 20%) (15 g),

rapidly disintegrating PVP (20 g),

potato starch (10 g),

silica gel (3 g),

maltodextrin (5 g),

microcrystalline cellulose (2 g),

water (0.5 g),

giving a total yield of 524.36 g.

A second mixture is prepared and used to form the slow-dissolving layer (LAYER B) thus obtained:

lyophilized blueberry (15 g),

microcrystalline cellulose (50 g),

titanium dioxide (10 g),

nucleic acids (50 g),

blueberry extract 25% (50 g),

copper gluconate (1.5 g),

zinc gluconate (12.3 g),

copper gluconate (1.5 g),

zinc gluconate (13.8 g),

selenium-containing yeast (9.5 g),

glutathione on yeast (15 g),

vitamin A 500,000 IU/g (4.63 g),

vitamin E 50% SD (25.6 g),

vitamin C EC 97% (99 g),

All these components are mixed and kneaded in a Z-type kneader together with melted hydrogenated palm oil (50 g).

The blend obtained is cooled to 12°C and granulated in an oscillating granulator equipped with a stainless steel plate having holes with a 2 mm diameter, giving a total yield of 408 g.

The two mixtures thus obtained can be compressed with an oval punch using a double-layered tablet-compressing machine (MANESTY BB3B) producing oval tablets with a weight of 0.932 g, in which the first layer weighing 0.524 g is fast-dissolving and the second layer weighing 0.408 g is gastro-resistant and slow-dissolving.

Example 2

Example 1 is repeated, except that the following components are used:

Layer A (FAST-DISSOLVING)

folic acid 98% (0.3 mg/cpr + 20%) (0.12 g)

vitamin B6 33.1/3 (1.5 mg + 20%) (1.8 g)

beta carotene 20% (4mg/cpr + 10%) (7.4 g)

vitamin E 50% SD (116 mg/cpr) (12.8 g)

vitamin C EC 97 (120 mg/cpr +20%) (49.5 g)
copper gluconate Cu 14% (1.2 mg/cpr) (6 g)
zinc gluconate Zn 13.4% (10 mg/cpr) (52.3 g)
selenium-containing yeast 2000 µg/g (55 µg/cpr) (19.3 g)
lactose CD (150 g)
microcrystalline cellulose (30 g)
water (4 g)
potato starch (30 g)
rapidly disintegrating PVP (Kollidon CL) (10 g)
silicagel (10 g)
maltodextrin (8g)giving a total of 391.22 g:
Layer B (SLOW-DISSOLVING)
sulfomucopolysaccharides (25 g)
Gingko biloba (30 g)
copper gluconate Cu 14% (3 g)
zinc gluconate Zn 13.4% (26.2 g)
selenium-containing yeast 2,000 µg/g (9.7 g)
microcrystalline cellulose (50 g)
red iron oxide (5 g)
folic acid (0.24 g)
vitamin B6 33.1/3% (3.6 g)
vitamin E 50% (25.6 g)
vitamin C EC 97% (99 g)
beta carotene 20% (14.8 g)
melted hydrogenated palm oil (72 g)
silica gel (0.5%),
giving a total of 0.358 g.

Double-layered tablets weighing 0.749 g are prepared, the first layer of which weighing 0.391 g is fast-dissolving and the second one weighing 0.358 g is slow-dissolving.

The tablets can then be coated with a solution of
10 % strength Klucel/water.

Example 3

Example 1 is repeated, except that the following components are used:

Layer A (FAST-DISSOLVING)	
acetylsalicylic acid	0.3 g
hydrogenated palm oil	0.1 g
lactose	0.2 g
Layer B (SLOW-DISSOLVING)	
acetylsalicylic acid	0.2 g
lactose	0.1 g
magnesium stearate	0.01 g
pre-dried corn starch	0.1 g

CLAIMS

1. Formulation for oral use in tablet form, containing at least one active principle with a pharmaceutical, dietary or alimentary action, characterized in that it contains, as the vehicle, at least one fat and/or phospholipid in an amount of between 5 and 30%, preferably between 10 and 20%, relative to the weight of the formulation.

2. Formulation according to Claim 1, characterized in that said at least one fat and/or phospolipid contains hydrogenated and non-hydrogenated fatty acids, either of synthetic or natural origin, having a chain comprising between 3 and 20 carbon atoms, preferably between 14 and 18 carbon atoms, or mixtures thereof.

3. Formulation according to Claim 1, characterized in that said at least one fat and/or phospholipid is selected from among cocoa butter, hydrogenated palm oil, hydrogenated vegetable fats such as peanut butter, animal fats such as lard, butter, bacon fat and in that said phospholipids are selected from among lecithins, preferably soya lecithins.

4. Formulation according to Claim 1, characterized in that said at least one fat and/or phospholipid is used in combination with alkali metal salts and/or alkaline earth metal salts of fatty acids having a chain comprising between 3 and 20 carbon atoms, preferably between 14 and 18 carbon atoms, or mixtures thereof.

5. Formulation according to Claim 1, characterized in that said at least one active principle is present in an amount of 70-95%, preferably 75-90%, relative to the weight of the formulation, and in that said at least one active principle and said at least one fat and/or phospholipid make up 100% by weight of the formulation.

6. Formulation according to Claim 1, characterized in that said at least one active principle with a therapeutic action is selected from among non-steroid and steroid anti-inflammatory drugs, tranquilizers, sleeping pills, anti-hypertensive, anti-histaminic and anti-asthmatic drugs and in that said at least one active principle with a dietary or alimentary action is selected from the group consisting of lactic acid microorganisms, beer yeasts, either as such or containing living cells, vitamins, minerals, amino acids, vegetable extracts, and derivatives thereof.

7. Formulation according to Claim 1, containing: (a) from 1 to 50% by weight, preferably from 30 to 50% by weight, of said at least one active principle with a pharmaceutical, dietary or alimentary action; (b) from 5 to 30% by weight, preferably from 20 to 30% by weight, of said at least one fat and/or phospholipid; (c) from 10 to 30% by weight, preferably from 20 to 30% by weight, of exicipients and/or adjuvants,

the sum of the components (a), (b) and (c) making up 100% by weight of the formulation.

8. Formulation according to Claim 7, characterized in that said excipients are selected from among starches, maltodextrin, microcrystalline cellulose, talcum-modified cellulose, calcium carbonate, milk proteins, calcium stearate, magnesium stearate, sodium stearate, soya proteins or suitable inert powders, PVP, and precipitated silica.

9. Process for the preparation of a formulation according to Claim 5 in which:

a) said at least one active principle is mixed with said at least one fat and/or phospholipid in the melted state in the weight proportions defined above;

b) the blend thus obtained is cooled to 5-20°C, preferably to 10°C-12°C, and then granulated using a granulator having holes with a diameter of between 1 and 4 mm, preferably between 1 and 2 mm;

c) the granules thus obtained are then compressed.

10. Process for the preparation of a formulation according to Claim 7 in which:

d) said at least one active principle is premixed at ambient temperature with said excipients and/or adjuvants in the weight proportions defined above;

e) the mixture thus obtained is mixed with said at least one fat and/or phospholipid in the melted state in the weight proportions defined above;

f) the blend thus obtained is cooled to 5-20°C, preferably to 10°C-12°C, and then granulated using a granulator having holes with a diameter of between 1 and 4 mm, preferably between 1 and 2 mm;

g) the granules thus obtained are then compressed.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/28526 A2

(54) Title: GASTRORESISTANT TABLETS FOR ALIMENTARY, DIETETIC AND THERAPEUTIC USE

(57) Abstract: A novel formulation for oral use is described, said formulation containing at least one active principle with a pharmaceutical, dietary or alimentary action, in combination with at least one fat and/or phospholipid in an amount of between 5 and 30 %, relative to the weight of the formulation; this formulation allows the slow release, over time, of the active principle under physiological conditions which simulate the digestive processes which normally take place in the stomach.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

PISTOLESI Roberto
DRAGOTTI & ASSOCIATI SRL
Galleria San Babila, 4/C
20122 Milano
ITALIE

RICEVUTO
- 9 NOV. 2001
Risp.

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	06.11.2001
Applicant's or agent's file reference 00 OT 22E	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IT00/00424	20/10/2000	21/10/1999

Applicant
TRUFFINI & REGGE'FARMACEUTICI S.R.L. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Longo, E Tel.+49 89 2399-8141

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
00 OT 22E		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IT00/00424	20/10/2000	21/10/1999
International Patent Classification (IPC) or national classification and IPC A61K9/20		
Applicant TRUFFINI & REGGE'FARMACEUTICI S.R.L. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/05/2001	06.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Baminger, U Telephone No. +49 89 2399 2176

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IT00/00424

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-9	as originally filed				

Claims, No.:

1-13	as received on	01/10/2001	with letter of	26/09/2001	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 5 and 10-12.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 5 and 10-12 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4, 6-9 and 13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-4, 6-9 and 13
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-4, 6-9 and 13

No: Claims

2. Citations and explanations
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The subject-matter of claims 5 and 10-12 is not clear to the extent that no meaningful opinion on the novelty, inventive step or industrial applicability of these claims can be formed (Article 34(4)(a)(ii) PCT).
Claim 5 refers to "said excipients...in the weight proportions defined above" without having mentioned excipients in any former claim.
Claim 10 is formulated as if it would depend on claim 6, however requires "at least one fat" instead of "at least one hydrogenated fatty acid". This renders the subject-matter of claim 10 broader than the subject-matter of claim 6. The same arguments apply to claims 11-12.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

5.1 The subject-matter of claim 1 is novel (Article 33(2) PCT) in view of the documents cited in the search report.

5.2 None of the prior art cited in the search report refers to the use of hydrogenated fatty acids in retarded release formulations. Therefore claim 1 of the present application appears to involve an inventive step (Art. 33 (3) PCT).

5.3 The same arguments apply mutatis mutandis to the independent claim 6.

CLAIMS

1. Process for the preparation of a retarded release formulation for oral use in tablet form, containing at least one active principle with a pharmaceutical, dietary or alimentary action and at least one hydrogenated fatty acid, as the vehicle, in amounts of between 5 and 30%, relative to the weight of the formulation, wherein:

(a) said at least one active principle is mixed with said at least one hydrogenated fatty acid in the melted state in the weight proportions defined above;

(b) the blend thus obtained is cooled to 5-20°C and then granulated using a granulator having holes with a diameter of between 1 and 4 mm;

(c) the granules thus obtained are then compressed.

2. The process according to claim 1, wherein said hydrogenated fatty acid is present in amounts between 10 and 20%, relative to the weight of the formulation.

3. The process according to claim 1, wherein the blend in point (b) is cooled to 10°C-12°C.

4. The process according to claim 1, wherein the blend in point (b) is granulated using a granulator having holes with a diameter of between 1 and 2 mm.

5. The process according to claim 1 wherein:

(d) said at least one active principle is premixed at ambient temperature with said excipients and/or adjuvants in the weight proportions defined above;

(e) the mixture thus obtained is mixed with said at least one fat and/or phospholipid in the melted state in the weight proportions defined above;

(f) the blend thus obtained is cooled to 5-20°C, preferably to 10°C-12°C, and then granulated using a granulator having holes with a diameter of between 1 and 4 mm, preferably between 1 and 2 mm;

(g) the granules thus obtained are then compressed.

6. A formulation obtainable by the process according to claims 1-5.

7. A formulation according to claim 6, characterized in that said at least one hydrogenated fatty acid has a chain comprising between 3 and 20 carbon atoms, preferably between 14 and 18 carbon atoms, or mixtures thereof.

8. A formulation according to claim 6, characterized in that said at least one hydrogenated fatty acid is hydrogenated palm oil.

9. A formulation according to claim 6, characterized in that said at least one active principle is present in an amount of 70-95%, preferably 75-90%, relative to the weight of the formulation, and in that said at least one active principle and said at least one hydrogenated fatty acid make up 100% by weight of the formulation.

10. A formulation according to claim 6, characterized by containing: (a) from 10 to 50% by weight, of at least one active principle with a pharmaceutical, dietary or alimentary action; (b) from 5 to 30% by weight of at least one fat and (c) exicipients and/or adjuvants, the sum of the components (a), (b) and (c) making up 100% by weight of the formulation.

11. A formulation according to claim 10, characterized by containing from 30 to 50% by weight of component (a).

12. A formulation according to claim 10, characterized by containing from 20 to 30% by weight of component (b).

13. A formulation according to claim 6, characterized in that said at least one active principle with a therapeutic action is selected from non-steroid and steroid anti-inflammatory drugs, tranquilizers, sleeping pills, anti-hypertensive, anti-histaminic and anti-asthmatic drugs and in that said at least one active principle with a dietary or alimentary action is selected from the group consisting of lactic acid microorganisms, beer yeasts, either as such or containing living cells, vitamins, minerals, amino acids, vegetable extracts, and derivatives thereof.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
00 OT 22E		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IT00/00424	20/10/2000	21/10/1999
International Patent Classification (IPC) or national classification and IPC A61K9/20		
Applicant TRUFFINI & REGGE'FARMACEUTICI S.R.L. et al.		

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   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/05/2001	06.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Baminger, U Telephone No. +49 89 2399 2176

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IT00/00424

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-9	as originally filed				

Claims, No.:

1-13	as received on	01/10/2001	with letter of	26/09/2001	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

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   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

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   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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   ☐ the entire international application.

   ☒ claims Nos. 5 and 10-12.

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 5 and 10-12 are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4, 6-9 and 13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-4, 6-9 and 13
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-4, 6-9 and 13

No: Claims

2. Citations and explanations
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The subject-matter of claims 5 and 10-12 is not clear to the extent that no meaningful opinion on the novelty, inventive step or industrial applicability of these claims can be formed (Article 34(4)(a)(ii) PCT).
Claim 5 refers to "said excipients...in the weight proportions defined above" without having mentioned excipients in any former claim.
Claim 10 is formulated as if it would depend on claim 6, however requires "at least one fat" instead of "at least one hydrogenated fatty acid". This renders the subject-matter of claim 10 broader than the subject-matter of claim 6. The same arguments apply to claims 11-12.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

5.1 The subject-matter of claim 1 is novel (Article 33(2) PCT) in view of the documents cited in the search report.

5.2 None of the prior art cited in the search report refers to the use of hydrogenated fatty acids in retarded release formulations. Therefore claim 1 of the present application appears to involve an inventive step (Art. 33 (3) PCT).

5.3 The same arguments apply mutatis mutandis to the independent claim 6.

CLAIMS

1. Formulation for oral use in tablet form, containing at least one active principle with a pharmaceutical, dietary or alimentary action, characterized in that it contains, as the vehicle, at least one fat and/or phospholipid in an amount of between 5 and 30%, preferably between 10 and 20%, relative to the weight of the formulation.

2. Formulation according to Claim 1, characterized in that said at least one fat and/or phospolipid contains hydrogenated and non-hydrogenated fatty acids, either of synthetic or natural origin, having a chain comprising between 3 and 20 carbon atoms, preferably between 14 and 18 carbon atoms, or mixtures thereof.

3. Formulation according to Claim 1, characterized in that said at least one fat and/or phospholipid is selected from among cocoa butter, hydrogenated palm oil, hydrogenated vegetable fats such as peanut butter, animal fats such as lard, butter, bacon fat and in that said phospholipids are selected from among lecithins, preferably soya lecithins.

4. Formulation according to Claim 1, characterized in that said at least one fat and/or phospholipid is used in combination with alkali metal salts and/or alkaline earth metal salts of fatty acids having a chain comprising between 3 and 20 carbon atoms, preferably between 14 and 18 carbon atoms, or mixtures thereof.

5. Formulation according to Claim 1, characterized in that said at least one active principle is present in an amount of 70-95%, preferably 75-90%, relative to the weight of the formulation, and in that said at least one active principle and said at least one fat and/or phospholipid make up 100% by weight of the formulation.

6. Formulation according to Claim 1, characterized in that said at least one active principle with a therapeutic action is selected from among non-steroid and steroid anti-inflammatory drugs, tranquilizers, sleeping pills, anti-hypertensive, anti-histaminic and anti-asthmatic drugs and in that said at least one active principle with a dietary or alimentary action is selected from the group consisting of lactic acid microorganisms, beer yeasts, either as such or containing living cells, vitamins, minerals, amino acids, vegetable extracts, and derivatives thereof.

7. Formulation according to Claim 1, containing: (a) from 1 to 50% by weight, preferably from 30 to 50% by weight, of said at least one active principle with a pharmaceutical, dietary or alimentary action; (b) from 5 to 30% by weight, preferably from 20 to 30% by weight, of said at least one fat and/or phospholipid; (c) from 10 to 30% by weight, preferably from 20 to 30% by weight, of exicipients and/or adjuvants,

Replaced by Rule 34

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
DRAGOTTI & ASSOCIATI SRL
Attn. PISTOLESI Roberto
Galleria San Babila, 4/C
20122 Milano
ITALY

Applicant's or agent's file reference 00 OT 22E	Date of mailing *(day/month/year)* 18/05/2001 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/IT 00/00424	International filing date *(day/month/year)* 20/10/2000
Applicant TRUFFINI & REGGE'FARMACEUTICI S.R.L. et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Petronella Vaassen-Elsackers

Form PCT/ISA/220 (July 1998)

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
00 OT 22E		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IT 00/ 00424	20/10/2000	21/10/1999
Applicant		
TRUFFINI & REGGE'FARMACEUTICI S.R.L. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IT 00/00424

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 305 604 A (QUEST VITAMINS) 16 April 1997 (1997-04-16) claims	1,3-8
X	US 4 374 082 A (R.HOCHSCHILD) 15 February 1983 (1983-02-15) claims examples column 2, line 62 - line 65 column 3, line 34 - line 45 column 4, line 3 - line 29	1,3,5-7
X	DE 39 14 622 A (E.FIEGERT-SEIBT) 8 November 1990 (1990-11-08) claims examples column 1, line 40 - line 46 column 2, line 55 - line 62	1,3,6,9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 May 2001	18/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Scarponi, U

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 35656 A (R.P.SCHERER) 20 August 1998 (1998-08-20) claims examples	1-10
A	WO 95 05808 A (ABBOTT) 2 March 1995 (1995-03-02) claims	1-10

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IT 00/00424

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2305604 A	16-04-1997	NONE	
US 4374082 A	15-02-1983	AU 8693682 A	24-02-1983
		EP 0072469 A	23-02-1983
		JP 58041815 A	11-03-1983
DE 3914622 A	08-11-1990	NONE	
WO 9835656 A	20-08-1998	AU 6221298 A	08-09-1998
		BR 9808641 A	23-05-2000
		EP 0973506 A	26-01-2000
		US 6156339 A	05-12-2000
WO 9505808 A	02-03-1995	US 5591451 A	07-01-1997